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SCIENCE SPOTLIGHT

Explaining HLA Immunodominance in Vaccine-Induced T-Cell Responses to HIV-1

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The development of an effective HIV vaccine has been hampered by difficulties in inducing a protective antibody response. This has shifted the focus of vaccine development to a T-cell based vaccine, but the failure of adenovirus-based HIV T-cell vaccines to prevent transmission or decrease viral load (STEP study) was also a setback for T-cell based vaccines. The T-cell response that will be elicited by a vaccine is difficult to predict because of immunodominance, which directs most CD8 T-cells towards only a few viral components. Researchers from the lab of Dr. Helen Horton, an affiliate investigator of the Vaccine and Infectious Disease Division, VIDD co-director Dr. Julie McElrath, and lead author David Friedrich from the McElrath lab, investigated some of the complex factors that govern immunodominance, and therefore vaccine responses.

The researchers studied vaccine responses in healthy HIV-seronegative participants from two previous clinical trials of candidate recombinant adenoviral vaccines, to determine which epitopes and HLA-molecules elicit HIV-specific CD8+ T-cell responses. HLA molecules are proteins found on the surface of most cell types and present viral peptides, or epitopes, to CD8+ T-cells. If the CD8+ T-cell recognizes the viral epitope in the context of a given HLA molecule, the CD8+ T-cell may become activated. The group found that some HLA alleles are preferentially utilized in optimal HIV-1 specific responses during vaccination (B27, B57, B35 and B14). Additionally, certain HIV-1 epitopes were targeted more than others, and binding assays demonstrated that these epitopes had significantly higher affinities for their corresponding HLA alleles. Previously, this group had shown that epitopes targeted early in HIV-1 infection corresponded with disease progression. In this study, the researchers examined the avidity of the T-cell receptor (TCR) and level of HLA surface expression. B35-specific T-cells were of higher avidity than cells restricted by other alleles, so this might explain why B35 is preferentially utilized during an immune response to this vaccine.

Interestingly, T-cells restricted by B27 were shown to have low avidity, but still dominate early in infection and after vaccination. To understand how this was possible, the group measured HLA surface expression on T-cells and found that B27 had a 45% higher cell surface expression level than other alleles tested. This might explain why B27-restricted T cells can dominate in early

vaccination despite low TCR avidity. These studies demonstrate that immunodominance plays a large role in shaping vaccine-induced responses, which will be an important consideration in the evolution of vaccine design.

[Friedrich D, Jalbert E, Dinges WL, Sidney J, Sette A, Huang Y, McElrath MJ, Horton H](#). 2011.

Vaccine-induced HIV-specific CD8+ T cells utilize preferential HLA alleles and target-specific regions of HIV-1. *Journal of Acquired Immune Deficiency Syndrome* 58:248-252.